DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

MEMORANDUM **Center for Biologics Evaluation and Research - Food & Drug Administration**
Office of Therapeutics Research and Review

DATE: December 19, 1997

FROM: Chairman, Biologic License Application Review Committee for Zenapax (humanized anti-interleukin 2 receptor monoclonal antibody) (BLA no. 97-0736)

THROUGH: Chief, Immunology & Infectious Disease Branch, DCTDA

and Director, Division of Clinical Trial Design and Analysis

CC: Director, Division of Monoclonal Antibodies, OTRR
Keith Webber, DARP, Regulatory Coordinator

TO: FILE BLA 970-736

SUBJECT: Clinical review, efficacy data, BLA 97-0736

A detailed review of the clinical efficacy data and related statistical analysis and additional information is attached.

Ezio Bonvini, M.D.
Adjunct Clinical Reviewer
DCTDA

Biological License Application no. 97-0736
Annotated Clinical Review

PRODUCT: **Zenapax®, daclizumab, humanized anti-TAC, a humanized monoclonal antibody of the IgG1 isotype diected against the alpha (p55) chain on the human interleukin 2 receptor.**

SPONSOR: **Hoffman LaRoche**

PROPOSED INDICATION:
In the prophylaxis of kidney transplant rejection as an add-on to triple (steroids, azathioprine, cyclosporine) or double (azathioprine, cyclosporine) background immunosuppressive regimens.
"...for the prophylaxis of acute organ rejection in patients receiving renal transplants. It is used concomitantly with an immunosuppressive regimen, including cyclosporine and corticosteroids."

REVIEWER: **Ezio Bonvini, M.D. - HFM-564**
Laboratory of Immunobiology, DMA, OTRR, CBER

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1. INTRODUCTION.

1.1. Material Reviewed.

- BLA 97-0736
  Date of submission: June 9, 1997, as a Priority Review BLA (six-month review).
  Final action date: December 9, 1997.
- IND 5949 (current, active IND).
- Telephone conversations with the sponsor of 9/3/97 and 9/4/97.

1.2. Background information:

The draft package insert from the sponsor's BLA original submission will be used as the basis for this review of the primary efficacy endpoint. Critical statements in the package insert will be analyzed and criticized. Additional information pertinent to the clinical use of Zenapax but not included in the draft package insert are reviewed in context. The package insert has been divided into several individual segments, each reported verbatim. These direct quotes from the draft package insert are indented and shown in *italic*. Following the primary endpoint analysis, all secondary endpoints are reviewed and analyzed in detail. The safety section of the BLA submission is covered in Dr. Jeffrey Siegel's review.

1.3. Clinical trials conducted with Zenapax in the prevention of acute renal allograft rejection

Protocol No.	Study Design	Zenapax Dose (mg/kg)	Dosing Regimen	Other Immuno-suppressive Drugs	Centers	No. Pts Enrolled
Phase III						
NO14874	Randomized, double-blind, placebo-controlled, multiple-dose	1.0	Once every other week; five doses	Cyclosporine, corticosteroids	19 (15 Europe, 2 Australia, 2 Canada)	275
NO14393	Randomized, double-blind, placebo-controlled, multiple-dose	1.0	Once every other week; five doses	Cyclosporine, corticosteroids, azathioprine	17 (11 US, 3 Canada, 3 Sweden)	260
Phase I						
NO14392	Randomized, open-label, multiple-dose	0.5 or 1.0	Once every week or once every other week; five doses	Cyclosporine, corticosteroid, azathioprine	2 (US)	19
NO15301	Randomized, double-blind, placebo-controlled, multiple-dose	1.0	Once every other week; five doses	Cyclosporine, corticosteroids, mycophenolate mofetil	5 (US)	76

2. CLINICAL REVIEW OF THE PRIMARY EFFICACY DATA.

2.1 Description of the Drug

2.1.1 Package insert: Segment no. 1.

DESCRIPTION: ZENAPAX contains Zenapax, an immunosuppressive monoclonal antibody produced by recombinant DNA technology. The sterile solution contains a humanized recombinant monoclonal antibody of the IgG1 isotype. Zenapax binds specifically to the Tac subunit of the IL–2 receptor that is expressed on the surface of activated lymphocytes.

The recombinant genes encoding Zenapax are a composite of human (90%) and murine (10%) antibody sequences. The human sequences were derived from the constant domains of human IgG1 and the variable framework regions of the Eu myeloma antibody. The murine sequences are derived from the complementarity–determining regions of the murine anti–Tac antibody. The molecular weight predicted from DNA sequencing is 144 kilodaltons.

ZENAPAX 25 mg/5mL is supplied as a clear colorless concentrate for further dilution and intravenous administration. Each milliliter of ZENAPAX contains 5 mg of Zenapax and 3.56 mg sodium phosphate monobasic monohydrate, 10.99 mg sodium phosphate dibasic heptahydrate, 4.6 mg sodium chloride, and 0.2 mg polysorbate 80 and may contain hydrochloric acid or sodium hydroxide to adjust the pH to 6.9.

2.1.2. **Reviewer's comment.** This portion of the draft insert is consistent with the product and manufacturing information contained in the CMC section of the BLA. For further information, please see the CMC review by the product reviewer, Dr. Barbara Rellahan.

2.2 Clinical Pharmacology

2.2.1. Package insert: Segment no. 2.

CLINICAL PHARMACOLOGY: Mechanism of Action: ZENAPAX contains Zenapax, a recombinant, humanized IgG1 anti–Tac antibody that functions as an interleukin–2 (IL–2) receptor antagonist. Zenapax binds with high affinity to the alpha, or Tac, subunit of the high–affinity IL–2 receptor complex and inhibits IL–2 binding and biological activity. Zenapax binding is highly specific for Tac, which is expressed on activated but not resting lymphocytes. Administration of ZENAPAX inhibits IL–2–mediated activation of lymphocytes, a critical pathway in the cellular immune response involved in allograft rejection.

2.2.2 **Reviewer's comment.** See the CMC review (Dr. Barbara Rellahan) for additional information. See pharmatox review (Dr. David Essayan) for additional information. Note that DacliXImab should be changed to DacliZUmab, in agreement wit the USAN convention for humanized antibodies.

2.3 Description of the Clinical Studies

2.3.1 Package insert: Segment no. 3.

Clinical Studies: *The safety and efficacy of ZENAPAX for the prophylaxis of acute organ rejection in renal allograft patients were assessed in two randomized, double–blind, placebo–controlled, multiple–dose, multicenter. These trials compared a dose of 1.0 mg/kg of ZENAPAX with placebo when each was administered as part of an immunosuppressive regimen containing either cyclosporine and corticosteroids (double–therapy immunosuppressive regimen) or cyclosporine, corticosteroids, and azathioprine (triple–therapy immunosuppressive regimen) to prevent acute rejection.*

2.3.2 **Study design and patient population.** Data from the two phase 3 studies provide the basis for the determination of efficacy of Zenapax in the prevention of acute rejection in renal allograft recipients. The two phase 3 studies shared a common study design. These studies were designed to investigate the efficacy and safety of adding Zenapax to standard two–drug (No. 14874) or three–drug (No. 14393) immunosuppressive therapy for preventing acute allograft rejection in patients receiving their first renal allograft from a cadaveric donor. Both studies were international, randomized, placebo–controlled, double–blind trials in recipients of first cadaveric renal allografts.

Phase 3 Studies: Inclusion Criteria

Inclusion Criteria	No.14874	No.14393
Age: ≥18 years	X	X
Gender: Men and nonpregnant women	X	X
Life expectancy: Not severely limited by diseases other than renal disease	X	X
Receiving first renal allograft Cadaveric donor	X	X
Patient (guardian) willing and able to give written informed consent	X	X

Phase 3 Studies: Exclusion Criteria

Exclusion Criteria	No.14874	No.14393
Previous renal allograft	X	X
Renal allograft from an HLA–identical living donor	X	X
Previously received IL–2–directed monoclonal antibody or other investigational agent interfering with Zenapax evaluation	X	X
Significant active infection	X	X
Positive lymphocytotoxic crossmatch (donor lymphocytes vs recipient serum)	X	X
Receiving any multiple–organ transplant	X	X
History of cancer within last 5 years (other than nonmelanoma skin cancer)	X	X
Known contraindication to Cyclosporine or systemic corticosteroids	X	X
Known contraindication to Azathioprine		X

Phase 3 Studies: Differences in Study Design

	No.14874	No.14393
Azathioprine	No	Yes
Steroid prophylaxis & treatment of rejection	Per institution	Specified dose and dosing schedule
CMV prophylaxis	Per institution; optional except for high–risk patients	Specified; required for all high–risk patients
Implantation biopsy	Optional by center	Required
Pharmacokinetics	Two centers	All US centers
Soluble IL–2 receptor alpha	Not done	All US centers
Anti–Zenapax antibodies	All centers	All US centers

2.3.3. **Concomitant medications.** All patients received an immunosuppressive regimen of double therapy (cyclosporine and corticosteroids, NO14874) or triple therapy (cyclosporine, prednisone, and azathioprine, NO14393) and either placebo or Zenapax (1.0 mg/kg) once every other week for a total of five doses beginning immediately before transplantation.

Phase 3 Studies: Concomitant Immunosuppressive Medications

	No.14874	No.14393
Immunosuppressive Prophylaxis		
Cyclosporine A	12 h pretrsplt to 24 h posttrsplt: 5 mg/kg IV. Subsequent doses: per institution therapeutic range.	12 h pretrsplt to 24 h posttrsplt: 5 mg/kg IV. Subsequent doses: per institution therapeutic range.
Prednisone or methylprednisolone	Per institution therapeutic practice.	Days 0–2: 7 mg/kg IV daily tapered to 2 mg/kg. Days 3–180: Tapered to 5–10 mg po daily.
Azathioprine		Day 0: 2–4 mg/kg IV or po. Subsequent doses: 1.5–2 mg/kg daily IV or po.
Treatment of Rejection		
First Line: Methylprednisolone	>1 day high–dose pulse per institution therapeutic practice. Tapered over 14 days to pre–rejection levels.	7 mg/kg IV for 3 days. Tapered over 14 days to pre–rejection levels.
Other antilymphocyte antibodies (OKT3, ATG)	Per institution therapeutic practice.	Per institution therapeutic practice.

Note that Cyclosporine A was used as part of the background immunosuppressive regimen in all completed trials of prevention of acute renal allograft rejection. CsA was used in both phase III trials efficacy trials.

Note that immunosuppressive steroid prophylaxis and CMV prophylaxis regimens were based on local institutional protocols in study No. 14874. They were pre-specified in the triple therapy trial

No. 14393. Hence, secondary analyses of the use of immunosuppressive therapies will reflect this fact.

2.3.4. **Follow-up**: Patients were followed for 1 year post-transplant for acute rejection and are to be followed for 3 years post-transplant for patient and graft survival, graft function, and lymphoproliferative disorders and other malignancies (ongoing, expected last patient follow-up February '99). Patients were assessed for efficacy, safety, pharmacokinetics, immunogenicity, and immunopharmacology (NO14393 only). A total of 275 patients were enrolled in Protocol NO14874 at 19 centers in Europe, Canada, and Australia, and 260 patients were enrolled in Protocol NO14393 at 17 centers in the United States, Canada, and Sweden.

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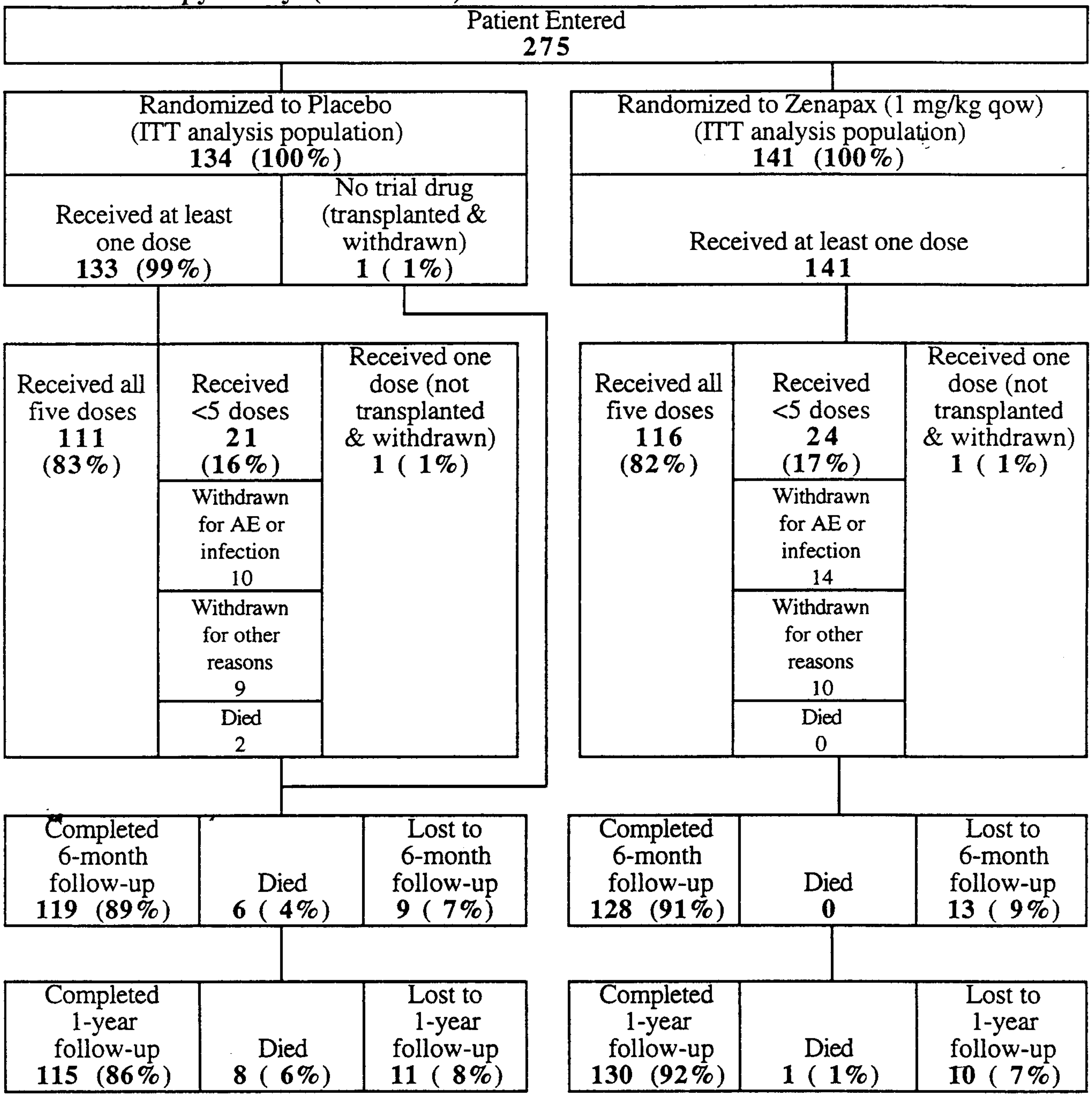
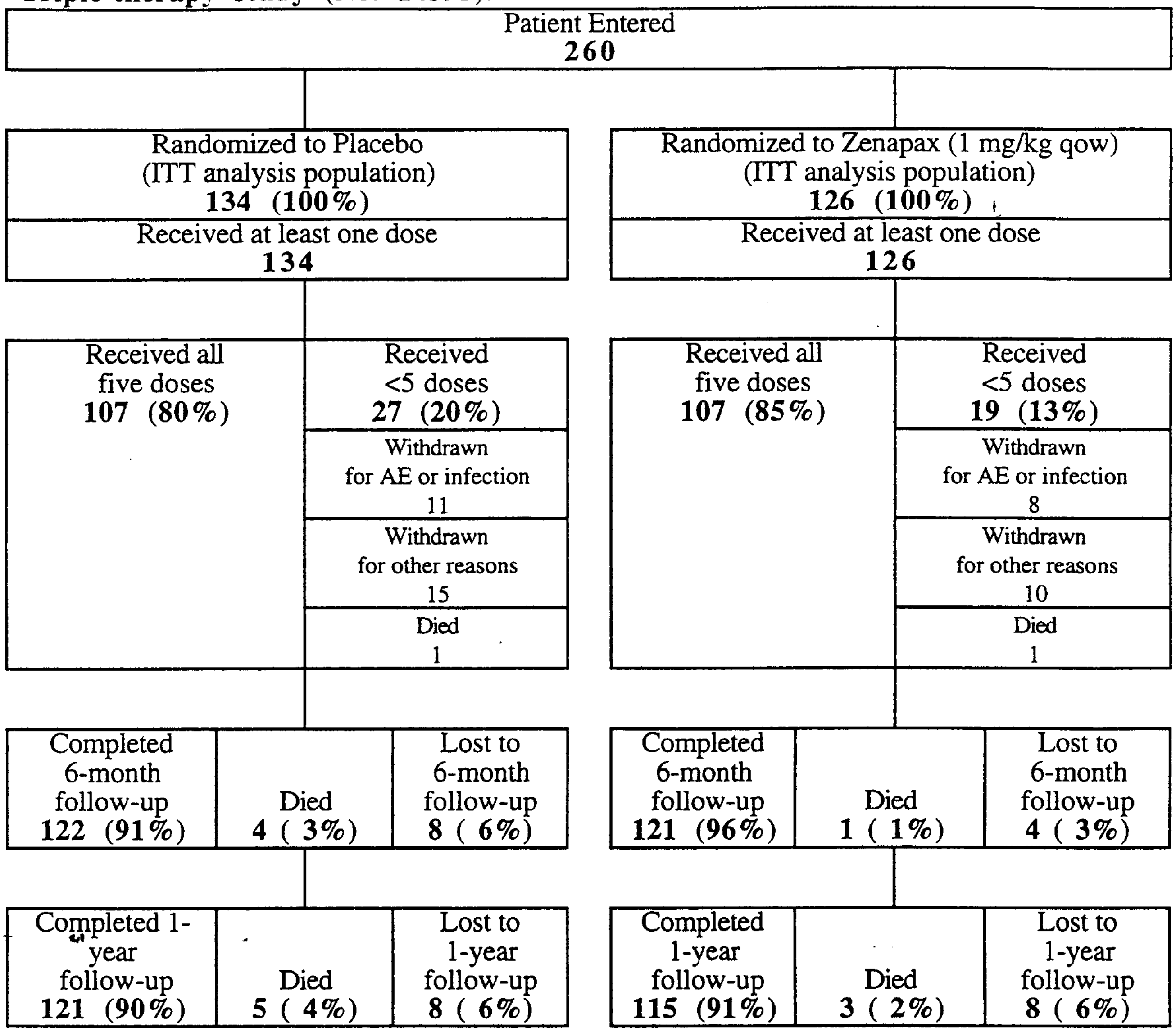
2.3.5. **Patient disposition**:

Double-therapy study (No. 14874):



One patient (———) randomized to the placebo group received a renal transplant but did not receive trial drug. Two patients, one in the HAT group (———) and one in the placebo group (———), received one dose of trial drug but were not transplanted. A total of 247 (90%) patients completed the 6–month follow–up and 245 (89%) patients completed the 1–year follow–up. Follow–up data were not available for 22 of the 275 (8%) patients at 6 months post-transplant and for 21 of the 275 (8%) patients at 1 year post-transplant.

Triple-therapy study (No. 14393):



A total of 243 (93%) patients completed the 6–month follow–up and 236 (91%) patients completed the 1–year follow–up. Follow–up data were not available for 12 of the 260 (5%) patients at 6 months post-transplant and 16 of the 260 (6%) patients at 1 year post-transplant.

Phase 3 studies: Premature Withdrawal and patients lost at follow-up.

	Study No.14874		Study No.14393	
	Placebo (N = 134)	**ZENAPAX (N = 141)**	**Placebo (N = 134)**	**ZENAPAX (N = 126)**
No. of patients withdrawn	23 (17%)	25 (18%)	27 (20%)	19 (15%)
No. of patients without follow-up data at 6 months post-transplant	9 (7%)	13 (9%)	8 (6%)	4 (3%)
No. of patients without follow-up data at 1 year post-transplant	11 (8%)	10 (7%)	8 (6%)	8 (6%)

The number of patients lost at the 6-month and 1-year follow-up was equal to or less then 9% of the patients enrolled in either arm of either study. The number of patients withdrawn, inclusive of patients that did not receive all five doses of medication, was less than 20% of the patients enrolled in either arm of either study. There was no imbalance between treatment arms in the fraction of patients withdrawn. The loss of patients at the 6-month and 1-year intervals was acceptable.

2.3.6 The Intent-to-treat (ITT) population included all patient enrolled and randomized to each treatment arm.

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2.3.7 **Patient demographics:**

Phase 3 studies: Demographic and baseline characteristics

	Study NO14874		Study NO14393	
	Placebo (N = 134)	**ZENAPAX (N = 141)**	**Placebo (N = 134)**	**ZENAPAX (N = 126)**
Donor & Patient Gender				
Male / Male	55 (41%)	65 (46%)	45 (34%)	41 (33%)
Male / Female	25 (19%)	20 (14%)	28 (21%)	31 (25%)
Female / Female	36 (27%)	40 (28%)	36 (27%)	33 (26%)
Female / Male	18 (13%)	15 (11%)	25 (19%)	21 (17%)
Unknown / Female	–	1 (1%)	–	–
Donor Age (years)				
No. of Pts.	134	138	134	126
Mean	42	39	36	35
Standard Error	1.5	1.3	1.4	1.4
Median	45	39	37	36
Min – Max	5 – 75	4 – 73	3 – 73	3 – 65
Patient Age (years)				
No. of Pts.	134	141	134	126
Mean	46	45	47	47
Standard Error	1.1	1.1	1.1	1.1
Median	47	46	47	47
Min – Max	18 – 73	18 – 67	18 – 80	18 – 70
Patient Weight (kg)				
No. of Pts.	134	141	134	125
Mean	69	71	75	76
Standard Error	1.1	1.3	1.4	1.6
Median	67	70	75	74
Min – Max	45 – 110	30 – 133	37 – 118	38 – 127
Patient Race				
Caucasian	127 (95%)	136 (96%)	81 (60%)	84 (67%)
Black	3 (2%)	2 (1%)	27 (20%)	24 (19%)
Oriental	1 (1%)	1 (1%)	6 (4%)	4 (3%)
Other	3 (2%)	2 (1%)	20 (15%)	14 (11%)

(continue)

Phase 3 studies: Demographic and baseline characteristics (cont.)

	Study No.14874		Study No.14393	
	Placebo (N = 134)	ZENAPAX (N = 141)	Placebo (N = 134)	ZENAPAX (N = 126)
Cold Ischemia Time (h)				
No. of Pts.	130	139	134	125
Mean	23	22	21	22
Standard Error	0.7	0.6	0.8	0.7
Median	22	21	19	20
Min – Max	5 – 50	9 – 50	3 – 51	6 – 54
Primary Cause of Renal Failure				
Glomerulonephritis	55 (41%)	61 (43%)	40 (30%)	33 (26%)
Polycystic & Other Hereditary Diseases	20 (15%)	21 (15%)	20 (15%)	24 (19%)
Diabetes Mellitus	10 (7%)	4 (3%)	29 (22%)	32 (25%)
Hypertensive Kidney Disease	6 (4%)	10 (7%)	19 (14%)	18 (14%)
Unknown Etiology	20 (15%)	17 (12%)	10 (7%)	9 (7%)
Pyelonephritis & Interstitial Nephritis	14 (10%)	18 (13%)	2 (1%)	5 (4%)
Other	9 (7%)	10 (7%)	14 (10%)	5 (4%)
Panel Reactive Antibodies				
No. of Pts.	127	137	134	125
Mean (%)	7	4	4	3
Standard Error	1.5	0.9	1	0.8
Median (%)	0	0	0	0
Min – Max (%)	0 – 78	0 –47	0 – 90	0 – 62
0% – 10%	108 (85%)	119 (87%)	121 (90%)	112 (90%)
11% – 49%	11 (9%)	18 (13%)	10 (7%)	12 (10%)
≥50%	8 (6%)	–	3 (2%)	1 (1%)
T-Cell Lymphocytotoxic Crossmatch				
Negative	134 (100%)	140 (99%)	132 (99%)	125 (99%)
Positive	–	1 (1%)	2 (1%)	–
Unknown	–	–	–	1 (1%)
HLA Mismatch (A, B, DR)				
0	8 (6%)	10 (7%)	8 (6%)	13 (10%)
1	19 (14%)	11 (8%)	8 (6%)	5 (4%)
2	22 (16%)	26 (18%)	13 (10%)	14 (11%)
3	34 (25%)	39 (28%)	20 (15%)	17 (13%)
4	20 (15%)	26 (18%)	27 (20%)	25 (20%)
5	16 (12%)	18 (13%)	28 (21%)	31 (25%)
6	5 (4%)	2 (1%)	20 (15%)	13 (10%)
CMV Serological Status				
Donor+ / Patient+	51 (38%)	55 (39%)	67 (50%)	42 (33%)
Donor+ / Patient–	27 (20%)	31 (22%)	31 (23%)	29 (23%)
Donor– / Patient+	32 (24%)	31 (22%)	24 (18%)	33 (26%)
Donor– / Patient–	14 (10%)	16 (11%)	10 (7%)	22 (17%)

There was no imbalance between arms of the double therapy study (no. 14874). The triple-therapy study (no. 14393) was well balanced in demographic factors, except for a statistically significant

differences in the CMV serological status of the donor–recipient pairs (p = 0.01, chi square test, sponsor's analysis). The intervention arm had more donor–recipient pairs with negative serology results for CMV and fewer donor–recipient pairs with positive serology results for CMV than the placebo group. Note, however, that the proportion of patients at highest risk for CMV (CMV–positive donor and CMV–negative recipient) was the same in the Zenapax and placebo groups (23%) in the triple–therapy study.
The double therapy study (no. 14874) included 19 centers from Europe, Australia, and Canada. As such, the demographic characteristics reflects that of the participating countries and differs from that typical of US studies. The triple therapy study (no. 14393) was conducted in the US, Canada, and Sweden. Patients were enrolled in this study between April 7, 1995 and February 10, 1996.

Triple-therapy phase 3 study (no. 14393): Participating centers.

	No of centers	No. of patients
United States	12	201 (77%)
Canada	3	26 (10%)
Sweeden	3	33 (13%)
Total	18	260

The 1996 Annual Report of the U.S. Scientific Registry of Transplant Recipient and the Organ Procurement and Transplantation Network (OPTN) included with the on-line databases of the United Network for Organ Sharing (UNOS).offers the most up-to-date information on age and race characteristics of cadaveric kidney transplant recipients in the US.

Demographic characteristics of US kidney transplant recipients (1).
Recipient age (years) at time of transplant (cadaveric kidney transplants).

Year	< 1	1-5	6-10	11-17	18-34	35-49	50-64	65+	Unk	Total
1988	0 (0.0%)	64 (0.9%)	79 (1.1%)	238 (3.3%)	2026 (28.0%)	2878 (39.8%)	1741 (24.1%)	202 (2.8%)	2	7230
1989	2 (0.0%)	55 (0.8%)	84 (1.2%)	205 (2.9%)	2061 (29.1%)	2790 (39.4%)	1687 (23.8%)	201 (2.8%)	1	7086
1990	5 (0.1%)	59 (0.8%)	79 (1.0%)	216 (2.8%)	2167 (27.8%)	3046 (39.1%)	1941 (24.9%)	269 (3.5%)	3	7785
1991	2 (0.0%)	45 (0.6%)	71 (0.9%)	174 (2.3%)	2110 (27.3%)	3060 (39.6%)	1954 (25.3%)	315 (4.1%)	1	7732
1992	1 (0.0%)	53 (0.7%)	50 (0.6%)	173 (2.2%)	2016 (26.2%)	3030 (39.4%)	2006 (26.1%)	366 (4.8%)	2	7697
1993	1 (0.0%)	51 (0.6%)	69 (0.8%)	172 (2.1%)	2048 (25.1%)	3207 (39.3%)	2224 (27.2%)	398 (4.9%)	0	8170
1994	1 (0.0%)	41 (0.5%)	77 (0.9%)	250 (3.0%)	1919 (22.9%)	3316 (39.6%)	2317 (27.6%)	460 (5.5%)	2	8383
1995	3 (0.0%)	42 (0.5%)	66 (0.8%)	226 (2.6%)	1922 (22.4%)	3399 (39.5%)	2439 (28.4%)	500 (5.8%)	1	8598

(UNOS OPTN/SR 1996 Annual Report)

Demographic characteristics of US kidney transplant recipients (2). Recipient race (cadaveric kidney transplants).

Year	White	Black	Hispanic	Asian	Other	Unk	Total
1988	4658 (64.5%)	1622 (22.5%)	563 (7.8%)	174 (2.4%)	206 (2.9%)	7	7230
1989	4598 (65.0%)	1566 (22.1%)	569 (8.0%)	174 (2.5%)	172 (2.4%)	7	7086
1990	5064 (65.2%)	1716 (22.1%)	587 (7.6%)	219 (2.8%)	177 (2.3%)	22	7785
1991	5003 (64.7%)	1711 (22.1%)	630 (8.2%)	242 (3.1%)	144 (1.9%)	2	7732
1992	4868 (63.5%)	1742 (22.7%)	645 (8.4%)	293 (3.8%)	115 (1.5%)	34	7697
1993	5235 (64.1%)	1831 (22.4%)	704 (8.6%)	274 (3.4%)	123 (1.5%)	3	8170
1994	5092 (60.9%)	2075 (24.8%)	746 (8.9%)	309 (3.7%)	136 (1.6%)	25	8383
1995	5175 (60.3%)	2060 (24.0%)	957 (11.1%)	285 (3.3%)	109 (1.3%)	12	8598

(UNOS OPTN/SR 1996 Annual Report)

Additional demographic characteristics pertinent to the Zenapax clinical trials can be obtained from the 1994 Report of Center Specific Graft and Survival Rates of the UNOS. Note that the data available are inclusive of kidney transplants from living donors, although they represent only a minor fraction (21.5%) of the total U.S. transplants.

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Demographic characteristics of US kidney transplant recipients (3).
US transplant 12/1/87-12/31/91 (living donor and cadaveric transplants).

Total transplant	39,930	(100%)
Donor type		
Cadaveric	31,333	(78.5%)
Living	8,583	(21.5%)
Not reported	4	
Recipient sex		
Female	15,869	(39.8%)
Male	24,017	(60.2%)
Not reported	7	
Cold Ischemia time		
0 -<10	10,523	(26.4%)
11-20	9469	(23.7%)
21-30	9839	(24.6%)
31-40	5,966	(14.9%)
>41	2,244	(5.6
Not reported	1879	(4.7%)
Insulin-dependent diabetes		
Yes	8,815	(22.1%)
No	31,055	(77.8%)
Not reported	50	(0.1%)
Peak Panel Reactive Antibodies (PRA) at transplant		
0	12,043	(30.2%)
1-9	12,063	(30.2%)
10-29	6,814	(17.1%)
30-59	3,281	(8.2%)
>60	4,530	(11.3%)
Not reported	1,189	(3%)
Level of mismatch		
0	3,446	(8.6%)
1	2,106	(5.3%)
2	5,865	(14.7%)
3	10,110	(25.3%)
4	9,205	(23.1%)
5	5,988	(15.0%)
6	2,024	(5.1%)
Not reported	1,176	(2.9%)

(UNOS 1994 Report of Center Specific Graft and Survival Rates)

The demographics of the triple therapy study (no. 14393) is consistent with that of the US kidney transplant population with respect to recipient age distribution, recipient's sex, cold ischemia time, incidence of diabetes as primary cause of renal failure, and PRA. The distribution of HLA mismatch status in study no. 143939 showed a slightly higher percentage of patients with 5 and 6 antigen mismatches compared to that of the US kidney transplant population. This was expected, since the available data for the US population includes living donors, the majority of whom are likely to be related donors. The percentage of whites (caucasians), and blacks is also consistent with the race distribution of transplant recipients in the US kidney transplant population. The "Other " category of study 14393 should include Hispanics, and is consistent with the representation of this patient category in the US recipient population. In summary, study 14393 is representative of the US kidney transplant recipient population. Note that race (black vs. otherwise), diabetes, and HLA mismatch status (1 or more, vs. 0) are the strongest negative predictors of graft survival.

2.3.8. **Stratifications**: patients were stratified for centers only in both phase 3 studies. There was no stratification for other factors in these trials.

2.3.9 **Attribution of patient category "Other"**: In the course of two telephone conversations (9/3/97 and 9/4/97) with HLR, it was confirmed that the race category "Other" in the patient demographic information includes patients of hispanic origin.

2.4 Dose and dosing regimen.

2.4.1 Package insert: Segment no. 4.

Dosing was initiated within 24 hours pretransplant, with subsequent doses given every 14 days for a total of five doses.

2.4.2 Reviewer's comment:

The dosing scheme was determined based on data from phase 1 and phase 2 studies. Dosing was established based on PK data and saturation of the IL2 receptor on circulating T lymphocytes. The current regimen achieves complete saturation of the IL2 receptor on circulating T lymphocytes for up to 120 days (4 months) from the beginning of treatment. Note that the IL2 receptor saturation persists even after circulating free antibody is no longer detectable in the blood. *In vitro* and *in vivo* data suggest that serum levels of 5 to 10 microg/mL are necessary for saturation of the IL2 receptor to block the responses of activated T lymphocytes.

2.5 Primary Efficacy Parameter.

2.5.1 Package insert: Segment no. 5.

The primary efficacy endpoint of both trials was the proportion of patients who developed a biopsy–proven acute rejection episode within the first 6 months following transplantation. As shown in Table 1, the incidence of biopsy–proven acute rejection in patients given a double–therapy immunosuppressive regimen was 28% in the ZENAPAX–treated group and 47% in the placebo–treated group. This 40% decrease in the incidence of acute rejection between treatment groups was statistically significant (p=0.001). In patients given a triple–therapy immunosuppressive regimen, the incidence of biopsy–proven acute rejection was 22% in the ZENAPAX–treated group and 35% in the placebo–treated group. This 37% decrease in the incidence of acute rejection between treatment groups was statistically significant (p=0.03).

Table 1 . Incidence of Biopsy–Proven Acute Rejection

	Double–Therapy Regimen *(cyclosporine and corticosteroids)*		***Triple–Therapy Regimen*** *(cyclosporine, corticosteroids, and azathioprine)*	
	Placebo (N=134)	*ZENAPAX (N=141)*	*Placebo (N=134)*	*ZENAPAX (N=126)*
Number of patients with biopsy–proven acute rejection	*63 (47%)*	*39 (28%)*	*47 (35%)*	*28 (22%)*
p–value	*0.001*		*0.03*	

2.5.2 **The primary efficacy analysis.** The primary endpoint is correctly identified in the text as "the proportion of patients who developed a biopsy–proven acute rejection episode within the first 6 months following transplantation". This is, therefore, the incidence of first biopsy proven rejection. The overall rejection rate (total number of rejection episodes per patient during the first 6 months) is a secondary endpoint, as it should be for the reason outlined below.
Rejection episodes are associated with significant morbidity (hospitalization, requirement for additional immunosuppression, increased risk of infection, etc.). Therefore, preventing rejection is of medical value. Patients experiencing a rejection have also been considered at a greater risk for losing their graft: experiencing a single rejection episode increases the risk of graft loss by a great extent. Additional rejection episodes further increase this risk, but to a lesser extent. Therefore, the major benefit of an effective immunosuppressive prophylactic regimen is to maintain the patients in rejection-free status. This benefit is lessened should the regimen decrease the overall number of rejections without affecting the fraction of rejection-free patients. By assessing the number of rejection-free patients, the primary endpoint of these studies is consistent with the current thinking of the role of rejection as a predictor of graft loss. The endpoint is also consistent with the recommendations of the BRMAC Meeting of December 8, 1994, pertaining to trial design of immunospppressive drugs in kidney transplantation. Note, however, the choice of a six-month interval for the primary endpoint is not in agreement with the ideal one-year interval recommended by the BRMAC. This shorter interval may be acceptable, however, providing that data pertaining to the durability of the effect be obtained and support the earlier endpoint.

. However, use of the investigational drug was not associated with decreased graft and/or patient survival rates in both studies (see below).
The incidence and severity of rejection at 1 and 3 years, which were to be based on allograft biopsies, were initially designed as secondary efficacy parameters. These endpoints were removed when the protocol was amended to make biopsies at 1 year and 3 years optional.
The diagnosis of acute rejection was made clinically using prospectively-defined parameters as clinical signs and symptoms of rejection:

- body temperature greater than 37.8C orally,
- graft swelling,
- graft tenderness,
- rise in serum creatinine,
- rise in blood pressure,
- oliguria,
- Altered renal blood flow as detected on a renal scan or ultrasound findings consistent with rejection.

2.5.3 **Statistical considerations**: Both studies were powered to detect a 20% absolute reduction in the primary efficacy parameter from 50% in the placebo arm to 30% in the daclizumab arm with at least 80% power at a two–sided significance level of 0.05. A rate of premature withdrawal of approximately 20% and a continuity correction were used in determining the sample size.
The expected placebo rejection rate of 50% was observed in the double-therapy study (No. 14874). The triple-therapy study (No. 14393), however, showed a 35% placebo rejection rate. The study was therefore underpowered to adequately detect the expected difference. The 35% rejection rate is consistent with current published reports for the triple-therapy regimen.

2.5.4 **Biopsy-proven rejection**. A biopsy to confirm the diagnosis of rejection in each patient was to be performed, according to the protocol, within 24 hours of initiating anti-rejection treatment. In a few cases, the biopsy to confirm the diagnosis of the first rejection episode was performed earlier or later (i.e., 24 before or after initiating anti-rejection treatment). The sponsor decided before the study was unblinded to use a window of 5 days before or after as the day of clinical diagnosis of rejection as a prerequisite for accepting the validity of the confirmatory biopsy. Although the biopsy specimens were to be assessed at the centers according to the simplified Banff schema[1] the biopsy assessments from the local sites that are provided in the report, the case report forms, and summaries are descriptive rather than graded according to the simplified Banff schema. All primary endpoint biopsies (6-month data) were retrospectively reviewed and rated for severity according to the Banff classification by a central reviewer, Dr. Kim Solez of the University of Alberta, Edmonton, Canada, one of the members of the Banff conference on allograft pathology. His central review was blinded.

Both protocols allowed for optional biopsies at 1 year post-transplant to assess the incidence of chronic rejection. The biopsies were to be performed within a time window of 3 months before or after the 1–year date post-transplant and reviewed locally. No central review of 1-year biopsies was planned or performed.

[1] (References:
Solez K, et al. International standardization of criteria for the histologic diagnosis of renal allograft rejection: The Banff working classification of kidney transplant pathology. *Kidney Int* 1993; 44: 411-22.
Solez K, et al. Report of the third Banff conference on allograft pathology (July 20-24, 1995) on classification and lesion scoring in renal allograft pathology. *Trans Proc* 1996; 28:441-4)

Incidence of First Biopsy-Proven Acute Rejection during the first 6 months of Kidney transplant.

	Triple-Therapy Regimen (Sponsor's analysis)		
	Placebo (N=134)	ZENAPAX (N=126)	
Number of patients with biopsy-proven acute rejection	47 (35%)	28 (22%)	
p-value*	0.03		

* Fisher's exact test, two-sided p-value.

2.5.7 **Central biopsy data analysis.** An analysis of the results of the central review of the biopsies was not provided by the sponsor. The sponsor presentation was limited to the degree of agreement between the central review and the local biopsy results. In the double-therapy study, the overall agreement between the local and central review was 93%. The results agreed for 94% of the Zenapax-treated patients and 91% of the placebo-treated patients. In the triple-therapy study, the agreement between the local and central review was 94% in both the daclizumab and placebo groups.

The central review provided grading of severity on all positive specimen, but no analysis of severity score was performed by the sponsor.

An analysis of the central review data was performed by CBER based on computerized data sets provided by the sponsor.

Phase 3 studies. Incidence of first biopsy–proven acute rejection during the first 6 months post-transplant: Central biopsy review data.

	Double–Therapy Regimen No. 14874 (cyclosporine and corticosteroids)		**Triple–Therapy Regimen No. 14393** (cyclosporine, corticosteroids, and azathioprine)	
	Placebo (N=134)	**ZENAPAX (N=141)**	**Placebo (N=134)**	**ZENAPAX (N=126)**
Number of patients with biopsy–proven acute rejection	55 (41%)	37 (26%)	41 (31%)	25 (20%)
p–value*	0.01		0.06	

* Fisher's exact test, two-sided p-value.

2.5.8 **Other supporting analyses related to the primary efficacy endpoint:**
The sponsor provided an analysis of treatment–by–center interaction for the primary endpoint: there was no evidence of inconsistency in the differences between treatments across centers. The statistically significant difference between treatments was also confirmed in both studies by using exact inference.
Biopsy–Proven plus Presumptive Acute Rejection. To corroborate the primary endpoint, the sponsor provided an analysis of the combined incidence of biopsy–proven rejection and presumptive rejection in the first 6 months post-transplant. A presumptive acute rejection episode was defined as a clinically diagnosed acute rejection episode that was treated with higher doses of methylprednisolone for >1 day (double-therapy study, NO14874) or with 7 mg/kg of methylprednisolone daily for 3 days (triple-therapy study, NO14393) or with at least 5 days of antilymphocyte antibody therapy but was not confirmed by a biopsy. The difference in the incidence of acute rejection between the two treatment arms remained significant in favor of Zenapax even if a rejection was not biopsy–proven and considered presumptive. This analysis was only conducted for the six-month interval. No one-year data are available.

Phase 3 studies: Biopsy–Proven or Presumptive Acute Rejection during the First 6 Months Post-transplant.

	Double–Therapy Regimen No. 14874 (cyclosporine and corticosteroids)		**Triple–Therapy Regimen No. 14393** (cyclosporine, corticosteroids, and azathioprine)	
	Placebo (N=134)	**ZENAPAX (N=141)**	**Placebo (N=134)**	**ZENAPAX (N=126)**
Number of Patients with Biopsy–Proven or Presumptive Acute Rejection	67 (50%)	48 (34%)	52 (39%)	32 (25%)
Pairwise Treatment Comparison				
p value*	0.006		0.035	
Odds ratio estimate of Zenapax to placebo**	0.48 (95% CI: 0.29-0.81)		0.56 (95% CI: 0.33-0.96)	
Treatment–by–Center Interaction				
p value ***	0.42		0.50	

*Cochran–Mantel–Haenszel test stratified by center.
**Odds of rejection on Zenapax to the odds of rejection on placebo, adjusted by center.
***Breslow and Day's test for homogeneity of odds ratio across centers.

The number of patients whose acute rejection episode was presumptive rather than biopsy–proven represented less than 20% of the patients with acute rejection. In the double–therapy study, the percentage of patients with presumptive rather than biopsy–proven acute rejection was higher in the Zenapax group (19%, 9 of 48 patients) than in the placebo group (6%, 4 of 67 patients) groups. In the triple–therapy study, the percentage of patients with presumptive rather than biopsy–proven acute rejection was only slightly higher in the Zenapax group (13%, 4 of 32 patients) than in the placebo group (10%, 5 of 52 patients).

Logistic regression analysis for prognostic factors affecting the primary endpoint of biopsy-proven rejection six months post-transplant: The sponsor conducted an exploratory analysis to examine the effects of various baseline prognostic factors on the incidence of biopsy–proven acute rejection at 6 months. The analysis was also conducted in-house, with similar results. The choice of covariates was based on known prognostic factors for graft and patient survival.

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Phase 3 studies: Multivariate logistic regression analysis of all factors examined for effect on biopsy–proven acute rejection six months pst-transplant.

	NO14874		NO14393	
	Odds Ratio	**P Value**	**Odds Ratio**	**P Value**
Treatment				
Placebo vs. Zenapax	0.36	0.0004	0.47	0.02
Patient Race				
Non–Black vs Black	n/a	n/a	1.18	0.67
Donor/Patient Sex				
M/M vs M/F	0.87	1.60	1.60	0.75
M/M vs F/M	0.19	0.31	0.54	0.88
M/M vs F/F	0.48	0.16	0.73	0.13
Patient Age (years)				
<40 vs 40–60	0.65	1.02	0.20	0.96
<40 vs >60	0.61	0.46	0.19	0.12
Donor Age (years)				
<18 vs 18–39	0.77	0.80	0.93	0.64
<18 vs 40 –60	0.70	0.91	1.08	0.67
<18 vs >60	2.61	0.87	0.38	0.22
Donor/Patient CMV Status				
–/– vs –/+	1.63	2.48	1.80	0.32
–/– vs +/–	0.06	0.19	0.25	0.62
–/– vs +/+	0.50	0.02	0.36	0.16
Cold Ischemia Time (hours)				
<21 vs ≥21	1.02	0.94	1.05	0.89
Panel–Reactive Antibodies (%)				
≤ 10 vs >10	1.37	0.45	0.32	0.09
HLA–A Mismatch				
0 vs 1–2	0.79	0.50	1.42	0.47
HLA–B Mismatch				
0 vs 1–2	0.87	0.73	2.37	0.14
HLA–DR Mismatch				
0 vs 1 – 2	2.43	0.007	1.75	0.28
Diabetes Mellitus				
No vs Yes	1.31	0.67	0.67	0.32

Multivariate logistic regression analysis of the data from the double–therapy study showed that the probability of developing biopsy–proven acute rejection was independently reduced by treatment with Zenapax (p =0.0004) and the absence of HLA–DR mismatches (p = 0.007) when all other factors were controlled simultaneously in the model. A similar analysis of the data from the triple–therapy study showed that the probability of developing biopsy–proven acute rejection was independently reduced by treatment with Zenapax (p = 0.02) when all other factors were controlled simultaneously in the model.

Treatment failure: CBER conducted an additional analysis by using an endpoint of "Treatment Failure", defined as the incidence of any of the following: first biopsy-proven acute rejection, death, or graft loss from any cause within the first 6 month after kidney transplantation. Note that such endpoint was NOT prospectively defined and was NOT used by the sponsor in any of the analyses presented. This all-inclusive definition of treatment failure is nonetheless helpful in establishing whether treatment with Zenapax is associated with an overall benefit for the transplanted patient. The data support a beneficial effect of Zenapax at 6 months and 1 year post-transplant if all events (rejection, graft loss, and patient deaths) are computed

Phase 3 studies: The Combined Incidence of Biopsy Proven First Rejection Episode, Graft Loss or Death (Treatment Failure).

	Double–Therapy Regimen No. 14874		Triple–Therapy Regimen No. 14393	
	Placebo N=134	**Zenapax N=141**	**Placebo N=134**	**Zenapax N=126**
Treatment Failure six months post-transplant				
Biopsy Proven Rejections	63 (47%)	39 (28%)	47 (35%)	30** (24%)
Graft loss or death without previous biopsy-proven rejections	11 (8%)	10 (7%)	7 (5%)	2 (2%)
Total	**74** (55%)	**49** (35%)	**54** (40%)	**32** (25%)
p-value*	<0.001		0.01	
Treatment Failure one year post-transplant				
Biopsy Proven Rejections	65 (49%)	39 (28%)	51 (38%)	35 (28%)
Graft loss or death without previous biopsy-proven rejections	13 (10%)	12 (9%)	7 (5%)	3 (2%)
Total	**78** (58%)	**51** (36%)	**58** (43%)	**37** (29%)
p-value*	<0.001		0.02	

Fisher's exact test, two-sided p-value.

2.5.9 **Durability of response**: The incidence and severity of rejection at 1 and 3 years, which were to be based on allograft biopsies, were initially designed as secondary efficacy parameters. These endpoints were eliminated when the protocol was amended to make biopsies at 1 year and 3 years optional. Data were nonetheless collected and a landmark analysis of efficacy is provided by the sponsor. After all patients had been followed for 6 months post-transplant, the data base was closed, the treatment codes were unblinded, and the 6–month analysis was performed. Investigators in the study remained blinded until all their patients had completed 1 year of follow–up post-transplant. Neither study, however, was designed or powered to detect a difference in acute rejection rates at 1 year.

The one-year data analysis is presented below. Six-month data have been included, for comparison purposes.

Phase 3 studies: Analysis of Biopsy–Proven Acute Rejection during the First Year Post-transplant.

	Double–Therapy Regimen No. 14874 (cyclosporine and corticosteroids)		**Triple–Therapy Regimen No. 14393** (cyclosporine, corticosteroids, and azathioprine)	
	Placebo (N=134)	**ZENAPAX (N=141)**	**Placebo (N=134)**	**ZENAPAX (N=126)**
Number of patients with biopsy–proven acute rejection: **6 months**	63 (47%)	39 (28%)	47 (35%)	28 (22%)
p–value	0.001		0.03	
No. of patients with biopsy–proven acute rejection: **1-year**	65 (49%)	39 (28%)	51 (38%)	35 (28%)
p value*	<0.001		0.09	

*Cochran–Mantel–Haenszel test stratified by center.

In the double–therapy study, the acute rejection rate at 1 year remained at 28% in the Zenapax group and increased to 49% in the placebo group. In the triple–therapy study, seven patients in the Zenapax group and four patients in the placebo group experienced their first biopsy–proven acute rejection during months 7 to 12 post-transplant. The 26% difference between the two treatment arms was no longer statistically significant (p = 0.09). This was largely due to a substantial increase from 22% to 28% in the Zenapax group in the first biopsy–proven acute rejection during months 7 to 12 post-transplant. This result challenges, at least in part, the sponsor's claim of durability of response in the case of use of Zenapax in the context of a triple-therapy immunosuppressive regimen.

2.5.10 **Severity of rejection**. The severity of rejection was not always computed by the local pathologist. The simplified Banff criteria, which rate rejection in three grade of severity, were to be adopted. Local pathologists, however, often used descriptive criteria without formally scoring the severity according to the Banff convention. The central review of the biopsy slides did include severity of rejection. The sponsor however, did not provide the analysis or am electronic tabulation of the data with this submission. Note that the original design included severity of rejection at 6 months, 1-year and 3 year. Both studies were amended to remove the 1- and 3-year endpoints.

2.5.11 **Summary**. The double therapy study (no. 14874) shows a higher incidence of rejection in the placebo arm compared to the triple-therapy study (no. 14393) by either local or central review of the biopsy results.

The addition of Zenapax (1 mg/kg qow for 5 dose) to either the double-therapy or triple-therapy regimen decreases the incidence of first rejection during the first 6 months of kidney tranplantation. The magnitude of the effect is similar in either study, with a decrease in the proportion of patients with rejection of 40% and 37%, respectively (33% and 35%, respectively, when the central biopsy review data are used). This difference is statistically significant in the double therapy study irrespective of whether local or central biopsy results are used. In the double therapy study, the power to detect a statistically significant difference was hampered by an unanticipated low rejection rate in the placebo arm. The study reached significance when the local review was used, although the inclusion in this analysis of two patients with potentially questionable data makes the comparison only marginally significant (p=0.06). The central review of the result in the triple theraphy study is only marginally significantly different (p=0.06). See below for further discussion of 1-year data.

3. CLINICAL REVIEW OF THE SECONDARY ENDPOINTS RELATED TO EFFICACY.

3.1 Planned secondary endpoints.

The sponsor planned prospectively 13 secondary parameters:

i. Time to the first acute rejection episode.
ii. Number of acute rejection episodes per patient in the first 6 months post-transplant.
iii. Number of patients with greater than one rejection episode in the first 6 months post-transplant.
iv. Graft failure in the first year and at 3 years post-transplant.
v. Time to graft failure.
vi. Patient survival in the first year and at 3 years post-transplant.
vii. Incidence of delayed graft function.
viii. Graft function as measured by glomerular filtration rate and serum creatinine level at 6 months, 1 year, and 3 years post-transplant.
ix. Cumulative dose of prednisone in the first 6 months post-transplant.
x. Cumulative dose of OKT3 or other anti-lymphocyte antibody therapy in the first 6 months post-transplant.
xi. Documented infections in the first 6 months post-transplant.
xii. Incidence of lymphoproliferative disorders during the first 6 months and at 1 year and 3 years post-transplant.
xiii. Incidence of other malignancies during the first 6 months and at 1 year and 3 years post-transplant.

The sponsor chose to present only a selected number of secondary efficacy parameters in the packagae insert, all of them at the 6-month interval. While some of the planned secondary endpoints are more related to safety (xi, xii, xiii), it should be noted that the data pertaining to graft failure and patient survival at 1 year post-transplant are critical to asses the safety and efficacy of the product. A full analysis of secondary endpoints was included with the BLA. Those related to efficacy are reviewed below.

3.2 Time to the first acute biopsy–proven acute rejection.

The sponsor presented a Kaplan-Meier probability estimate of rejection with data censored at 6 and 12 months. A stratified logrank test was then used to calculate the significance. With data censored at six months, p values with regard to this endpoints were 0.0001 for the double-therapy study and 0.008 for triple-therapy study. At 1 year post-transplant the p value using the stratified logrank test was 0.0001 for the double-therapy study and 0.022 for the triple-therapy study.
A conditional probability strategy is a valid means of estimating the probability of rejection. The use of a logrank test for total curve comparison is acceptable as a means of total curve comparison for the double-therapy study (no. 14874), in which the two curves appear to be substantially

parallel after the first three months. In the case of the triple therapy study (no. 14393), however, Kaplan-Meier curves cannot be easily compared. The log rank method of curve comparison assumes that the hazard rate in one arm is proportional to the other, a situation that may not be true for the triple-therapy study. See the statistical analysis report for additional analysis and modeling of the Kaplan-Meier curves. In conclusion, there is a suggestion that, while there are fewer patients at risk in the treatment arm than in the placebo arm of the triple therapy study, the period during which these patients are at risk for rejection lasted longer in the treatment arm
Censoring the data at 6 months is arbitrary and may offer a biased estimate of the real probability of rejection. One year data are therefore presented below. Note that the late surge in probability of rejection is driven by one or two episodes and should not necessarily be interpreted as an indication of lack of response durability in the triple-therapy study.

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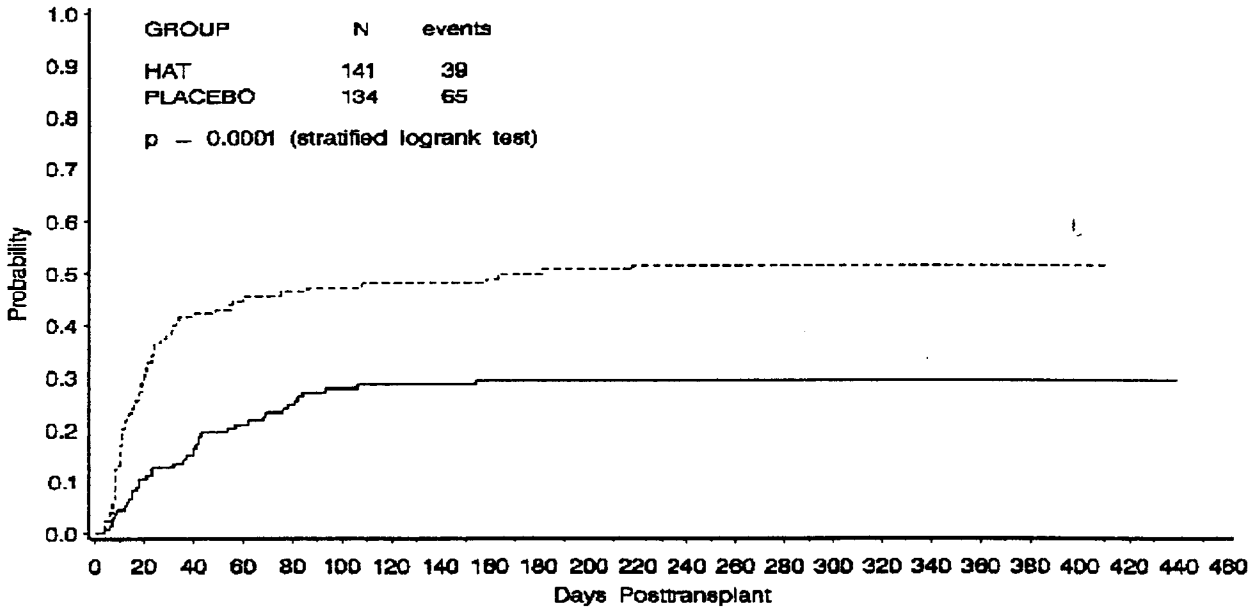
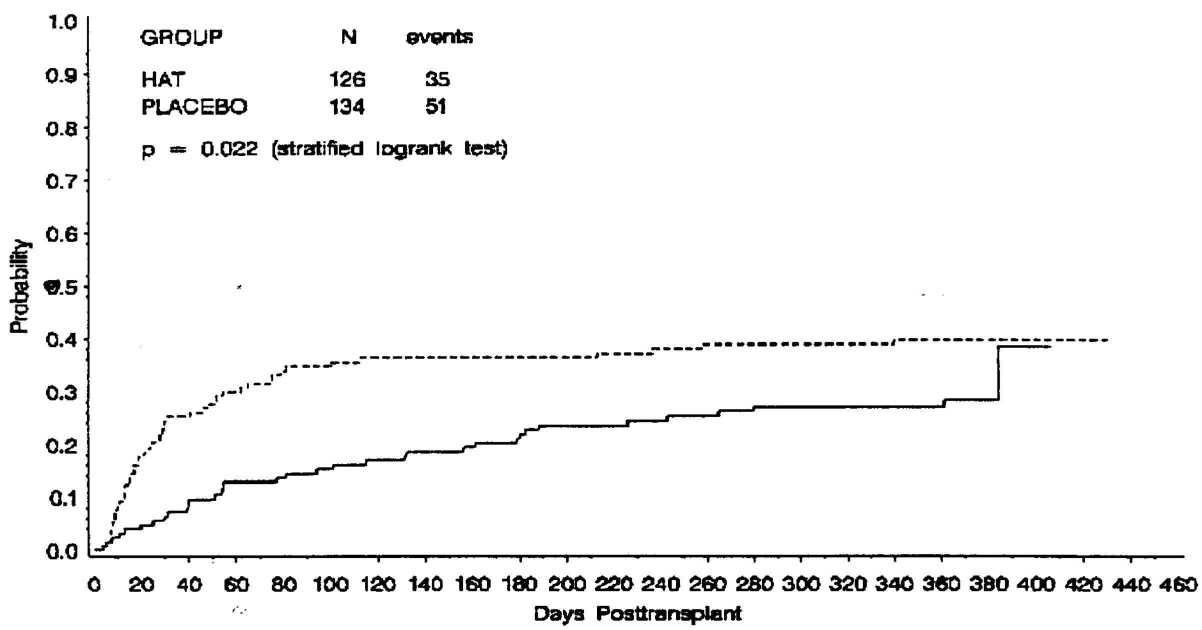


Kaplan–Meier Estimate of the Cumulative Probability of Biopsy–Proven Acute Rejection Episode during the First Year Post-transplant in NO14874.



Kaplan–Meier Estimate of the Cumulative Probability of Biopsy–Proven Acute Rejection Episode during the First Year Post-transplant in NO14393.

The sponsor provided additional descriptive analysis of the time to biopsy-proven rejection. The data are consistent with Zenapax delaying the first rejection episode even in the subset of patient who developed a rejection during the first 6 months post-transplant.

Analisys of time to biopsy-proven acute rejection.

	Study NO14874		Study NO14393	
	Placebo (N = 134)	ZENAPAX (N = 141)	Placebo (N = 134)	ZENAPAX (N = 126)
Time to Biopsy-Proven Acute Rejection during the First 6 Months Post-transplant				
25th percentile (days)	17	81	31	>183
Median (50th percentile, days)	181	>183	>183	>183
Probability of rejection at 6 months*	0.51	0.29	0.36	0.24
Subset of patients with biopsy-proven rejection during the first 6 months post-transplant				
Median (days)	15	36	20	54
Min – Max (days)	3 - 162	3 – 153	1 – 111	3 – 181
Time to Biopsy-Proven Acute Rejection during the First 12 Months Post-transplant				
25th percentile (days)	17	81	31	243
Median (50th percentile, days)	181	>364	>384	>384
Probability of rejection at 1 year*	0.51	0.29	0.40	0.28

* Kaplan–Meier estimate of probability of developing biopsy–proven acute rejection at 1 year.

Note, however, that the Kaplan-Meier probability estimate curves indicate that probability of rejection is nearly identical for both placebo and Zenapax-treated patients in the triple-therapy study (no. 14393) at 392 days.

3.3 Number of acute rejection episodes per patient in the first 6 months post-transplant and the Number of patients with greater than one rejection episode in the first 6 months post-transplant.

The phase 3 protocols did not provide definitive criteria for determining the number of rejection episodes. The criteria used in additional analyses, therefore, reflect those adopted for the definition of presumptive rejection. An acute rejection episode was defined as an event which was characterized by at least one of the clinical signs and symptoms listed earlier in this review and which resulted in a course of treatment either with methylprednisolone (7 mg/kg intravenously daily) for 3 days or with antilymphocyte antibody therapy for at least 5 days. Whether a rejection was a new episode or prolongation of an ongoing episode was left to the discretion of the investigator. Biopsy of steroid–resistant rejection and any subsequent rejection episodes was also at the discretion of the investigator.

The sponsor did collect data for individual rejection episodes during the 7-12-month interval. The analysis presented, however, is limited to the first 6-month interval. The sponsor provided a combined analysis of the number of acute rejection episodes per patient and the number of patients with equal or greater than one rejection episode in the first 6 months post-transplant. The data appear to support superiority of the Zenapax -treated arm, with respect to the number of patients experiencing one or more rejections and the average number of rejection.

Phase 3 studies: Number of Acute Rejection Episodes per Patient during the First 6 Months Post-transplant

	Study NO14874		Study NO14393	
	Placebo (N = 134)	ZENAPAX (N = 141)	Placebo (N = 134)	ZENAPAX (N = 126)
No. of pts with biopsy-proven or presumptive rejection	67 (50%)	48 (34%)	52 (39%)	32 (25%)
Patients with ≥1 acute rejection episode				
1	38 (28%)	30 (21%)	34 (25%)	23 (18%)
2	18 (13%)	16 (11%)	12 (9%)	8 (6%)
3	7 (5%)	–	5 (4%)	1 (1%)
4	4 (3%)	1 (1%)	1 (1%)	–
6	–	1 (1%)	–	–
No. of acute rejections per patient				
Mean	0.83	0.51	0.57	0.33
Standard error	0.09	0.07	0.07	0.06
Median	0.50	0	0	0
Range	0 – 4	0 – 6	0 – 4	0 – 3
P value*	0.004		0.01	

*Analysis of variance with treatments and centers as main effects.

By using the full ITT population in the denominator, however, the data are strongly influenced by the lower number of rejections in the Zenapax treated arm. An informative analysis is obtained by excluding the rejection-free patients, to obtain the distribution of rejection and rejection frequency among those patients that experienced one or more rejection episodes.

Phase 3 studies: CBER's Analysis of Acute Rejection Episodes per Patient during the First 6 Months Post-transplant

	Study NO14874		Study NO14393	
	Placebo	ZENAPAX	Placebo	ZENAPAX
No. of pts with biopsy-proven or presumptive rejection	N = 67	N = 48	N = 52	N = 32
Patients with ≥1 acute rejection episode: Data normalized per no. of patients with biopsy proven or presumptive rejection.				
1	38/67 (57%)	30/48 (63%)	34/52 (65%)	23/32 (72%)
2	18/67 (27%)	16/48 (33%)	12/52 (23%)	8/32 (25%)
3	7/67 (11%)	-	5/52 (10%)	1/32 (3%)
4	4/67 (6%)	1/48 (2%)	1/52 (2%)	-
6	-	1/48 (2%)		-
No. of acute rejections per patient				
Mean	1.66	1.50	1.47	1.30
Range	1 – 4	1 – 6	1 – 4	1 – 3

This analysis addresses whether Zenapax has a positive impact on those patients that experienced a rejection. The descriptive statistics suggest that Zenapax-treated patients that had experienced a rejection did not have an increased probability to experience multiple rejections compared to placebo-treated patients.

3.4 Graft failure in the first year post-transplant and the Time to graft failure.

These endpoints have been analyzed together. Neither study was formally designed to establish equivalence of treatment on graft survival at one year nor were they powered to detect a difference in graft survival. The sponsor presented in the BLA separate analyses for the 6-month and 12-month intervals. . While the data at the 12-month interval are more clinically relevant, the separate analysis allows for an understanding of the events that took place during 7-12 months after transplantation. Appropriately, a definition that included the need for chronic dialysis (≥6 consecutive weeks), transplant nephrectomy, retransplantation, or death, including death with a functioning graft was used for graft loss.

Phase 3 studies: Graft Survival at 6 Months and 1 Year Post-transplant

	Study NO14874		Study NO14393	
	Placebo (N = 134)	**ZENAPAX** (N = 141)	**Placebo** (N = 134)	**ZENAPAX** (N = 126)
Six Months Post-transplant				
No. of alive pts with functioning graft	115 (86%)	128 (91%)	122 (91%)	123 (98%)
No. of Pts with Graft Loss***	19 (14%)	13 (9%)	12 (9%)	3 (2%)
P value	0.22*		0.023**	
One Year Post-transplant				
No. of alive pts with functioning graft	111 (83%)	124 (88%)	121 (90%)	120 (95%)
No. of Pts with Graft Loss***	23 (17%)	17 (12%)	13 (10%)	6 (5%)
P value	0.300*		0.078*	
Events during months 7-12 Post-transplant				
No. of Pts with Graft Loss***	4 (3%)	4 (3%)	1 (1%)	3 (2%)

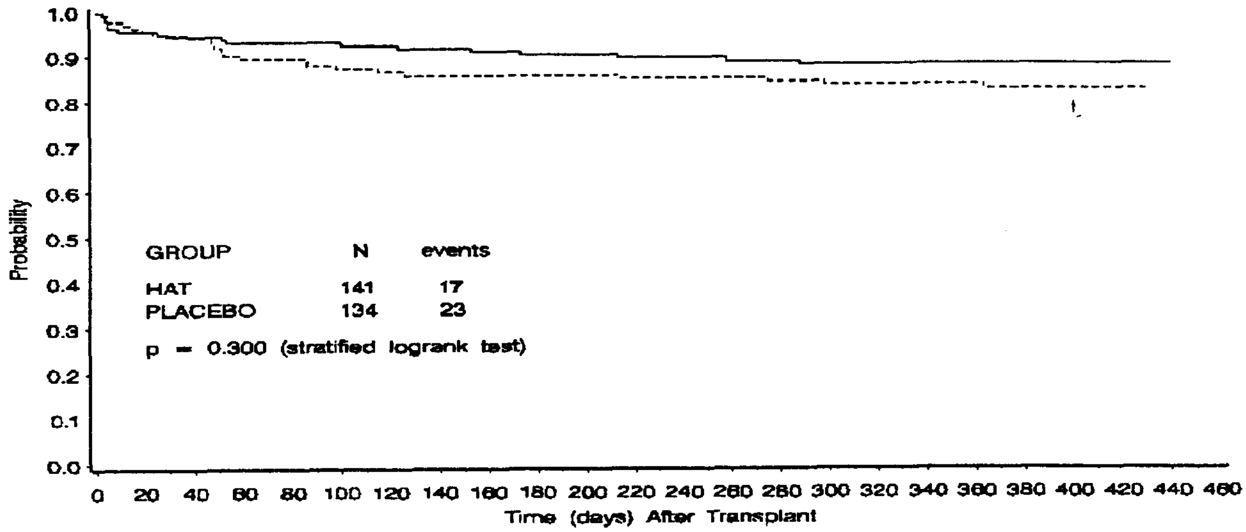
*Stratified logrank test from Kaplan-Meier analysis of data censored at 6 months.

**Unstratified logrank test Kaplan-Meier analysis of data censored at 1 year.

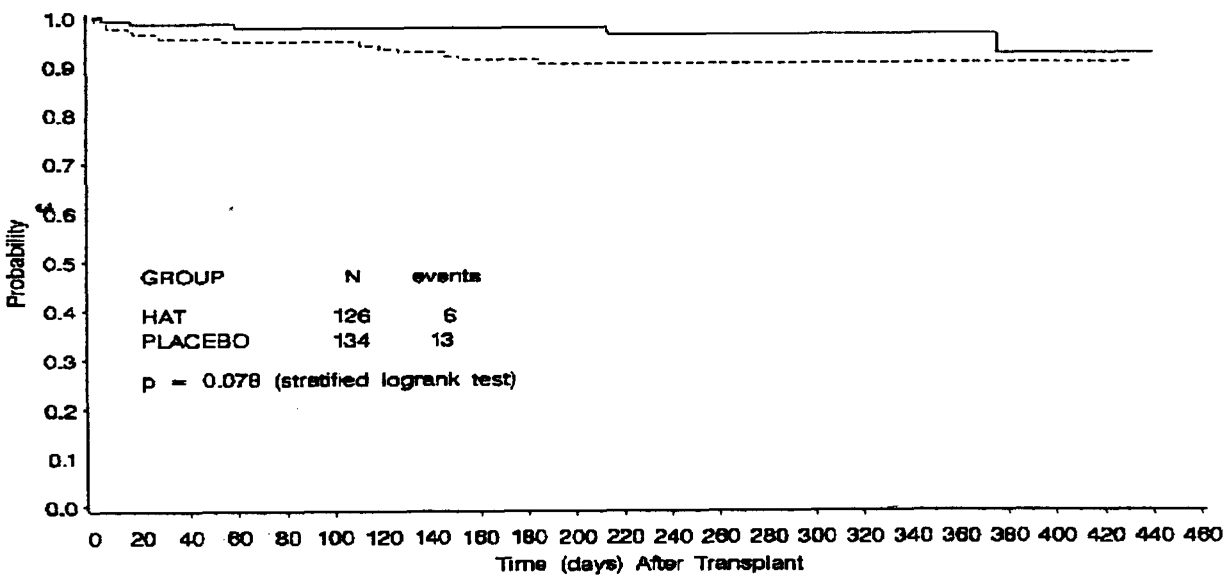
*** Graft loss was defined as the institution of chronic dialysis (≥6 consecutive weeks), transplant nephrectomy, retransplantation, or death (including death with a functioning graft).

For the double-therapy study (no. 14874), the vast majority of the events occurred during the first six months in either arm, with a non-significative advantage for the Zenapax treatment arm. The same was true for the placebo arm of the triple-therapy study (no. 14393). In the Zenapax arm of the triple-therapy study, however, as many events occurred during months 7-12 after transplantation as during the first six months after transplantation. This finding raises some concern that the effect of Zenapax may be transient in the context of a triple-therapy immunosuppressive regimen. There are few data and no firm conclusion can be established from these analyses, however. Furthermore, the differences are always in favor of the investigational drug.

The sponsor also presented Kaplan-Meier conditional probability estimates of graft survival with data censored at 6 and 12 months for both studies. Curve comparison (logrank analysis) with data censored at 6 months post-transplant suggested a significant difference in favor of treatment (see p values of above table). Censoring of the data at 6 months is arbitrary, however, and only the data pertaining to the 12 month interval are reviewed here. As for the probability of rejection, the data pertaining to the triple-therapy study (no. 14393) are affected by a late surge in graft loss, albeit not of the same magnitude observed for the rejection episodes. In this case too curve comparison is problematic, because the hazard rates are not constant over time. Nonetheless, log-rank analysis of Kaplan-Meier probability estimates show no significant difference between treatments. Although not significantly different, graft survival is in favor of Zenapax. This result addresses any potential concern pertaining to pertaining to a potential negative impact of added immunosuppression on the long-term fate of the allograft.



Kaplan–Meier Estimate of the Probability of Graft Survival during the First Year Post-transplant in NO14874



Kaplan–Meier Estimate of the Probability of Graft Survival during the First Year Post-transplant in NO14393

Phase 3 studies: Incidence and Primary Reason for Graft Loss during the First 6 Months and 1 Year After Transplantation

	Study No.14874		Study No.14393	
	Placebo (N = 134)	ZENAPAX (N = 141)	Placebo (N = 134)	ZENAPAX (N = 126)
Graft Loss during the first six months post-transplant				
No. of Pts with Graft Loss*	19 (14%)	13 (9%)	12 (9%)	3 (2%)
Primary Reasons for Graft Loss				
Technical	3 (2%)	7 (5%)	3 (2%)	2 (2%)
Cortical necrosis	–	–	1	–
Graft thrombosis	–	–	–	1
Problems with venous anastomoses	–	–	1	–
Renal vein thrombosis	2	3	1	1
Renal artery thrombosis	1	3	–	–
Hemorrhage from biopsy site	–	1	–	–
Death with a functioning graft	5 (4%)	–	4 (3%)	1 (1%)
Acute rejection	5 (4%)	1 (1%)	1 (1%)	–
Primary nonfunction	4 (3%)	2 (1%)	1 (1%)	–
Infarcted kidney	–	1 (1%)	2 (1%)	–
Atheromatous disease of renal artery	–	1 (1%)	–	–
Chronic rejection	–	1 (1%)	–	–
Malignancy in allograft	1 (1%)	–	–	–
Noncompliance	–	–	1 (1%)	–
Recurrence of original renal disease	1 (1%)	(1%)	–	–
Graft Loss during the first year post-transplant				
No. of Pts with Graft Loss*	23 (17%)	17 (12%)	13 (10%)	6 (5%)
Primary Reasons for Graft Loss				
Technical	3 (2%)	8 (6%)	3 (2%)	2 (2%)
Cortical necrosis	–	–	1	–
Graft thrombosis	–	–	–	1
Problems with venous anastomoses	–	–	1	–
Renal vein thrombosis	2	3	1	1
Renal artery thrombosis	1	4	–	–
Hemorrhage from biopsy site	–	1	–	–
Death with a functioning graft	7 (5%)	–	5 (4%)	3 (2%)
Acute rejection	5 (4%)	1 (1%)	1 (1%)	–
Primary nonfunction	4 (3%)	2 (1%)	1 (1%)	–
Infarcted kidney	–	1 (1%)	2 (1%)	–
Atheromatous disease of renal artery	–	1 (1%)	–	–
Chronic rejection	2 (1%)	3 (2%)	–	1 (1%)
Malignancy in allograft	1 (1%)	–	–	–
Noncompliance	–	–	1 (1%)	–
Recurrence of original renal disease	1 (1%)	1 (1%)	–	–

* Graft loss was defined in the protocol as the institution of chronic dialysis (≥6 consecutive weeks), transplant nephrectomy, retransplantation, or death (including death with a functioning graft).

The primary reasons for graft loss during the first 6 months post-transplant in the placebo group was death with a functioning graft. The most frequent reason for graft loss in the Zenapax group was technical surgical complications. Seven to twelve months after transplantation, an additional eight patients in the double–therapy study (four in each treatment group) and an additional four patients in the triple–therapy study (three in the Zenapax group and one in the placebo group) lost their grafts. The primary causes of graft loss in these 12 patients were death with a functioning graft (five patients), chronic rejection (five patients), renal artery thrombosis (one patient), and recurrence of original renal disease (one patient).

More graft losses from rejection (acute or chronic) were seen in the placebo group than in the Zenapax group in both studies during the first year post-transplant. In the double–therapy study, rejection was either the primary or secondary cause of graft failure in four patients in the Zenapax group and nine patients in the placebo group. In the triple–therapy study, one patient in the Zenapax group lost his graft because of rejection, while rejection was either the primary or secondary cause of graft failure in four patients in the placebo group. The results are tabulated by CBER below.

Phase 3 trials: Rejection-related graft losses during the first year post-transplant.

	Study NO14874		Study NO14393	
	Placebo (N = 134)	ZENAPAX (N = 141)	Placebo (N = 134)	ZENAPAX (N = 126)
Nunber of patients with graft loss	23 (17%)	17 (12%)	13 (10%)	6 (5%)
Total rejection-related Graft losses	9 (7%)	4 (3%)	4 (3%)	1 (1%)
Acute rejection as primary or Secondary cause of graft loss	6 (4%)	1 (1%)	4 (3%)	–
Chronic rejection as primary or Secondary cause of graft loss	3 (2%)	3 (2%)	–	1 (1%)

CBER computed the values for the triple-therapy study (no. 14393) in the following table, in order to look at the distribution of graft losses and deaths at 6 and 12 months post-transplant. The data have been delineated into two categories: rejection-free patients and patients who had experienced a previous rejection at any time. Note that, in the case of patients who experienced a previous rejection, the rejections in question occurred all during the first 6 months. The tabulation shows that of all the patients who died or experienced a graft loss, approximately 50% had a previous rejections and 50% were rejection-free. Therefore, the fraction of patients that are rejection-free or those that have experienced one or more rejections is equally represented among patients who died or lost their graft.

Triple-therapy phase 3 study: Distribution of patients who lost their graft or died while on trial.

	Placebo N=134	Zenapax N=126
First six-months post-transplant		
Alive patients who lost their graft:		
with previous biopsy-proven rejection	4 (3%)	-
without previous biospy-proven rejection	4 (3%)	2 (2%)
Total	**8 (6%)**	**2 (2%)**
Deaths while on trial:		
with previous biopsy-proven rejection	2 (1%)	1 (1%)
without previous biospy-proven rejection	2 (1%)	-
Total	**4 (3%)**	**1 (1%)**
Total graft loss and patient deaths		
with previous biopsy-proven rejection	5 (4%)	1 (1%)
without previous biospy-proven rejection	7 (5%)	2 (2%)
Total	**12 (9%)**	**3 (2%)**
First year post-transplant		
Alive patients who lost their graft:		
with previous biopsy-proven rejection	4 (3%)	1 (1%)
without previous biospy-proven rejection	4 (3%)	2(2%)
Total	**8 (6%)**	**3 (2%)**
Deaths while on trial:		
with previous biopsy-proven rejection	2 (1%)	2 (2%)
without previous biospy-proven rejection	3 (2%)	1 (1%)
Total	**5 (4%)**	**3 (2%)**
Total graft loss and patient deaths		
with previous biopsy-proven rejection	6 (4%)	3 (2%)
without previous biospy-proven rejection	7 (5%)	3 (2%)
Total	**13 (10%)**	**6 (4%)**

Triple-therapy phase 3 study (No. 14393): Distribution of graft loss or patient deaths amongst rejection positive and rejection-free patients.

	Placebo	Zenapax
First six-months post-transplant		
Number of patients with biopsy-proven rejection	N = 47	N = 28
Graft loss or deaths among pts. with previous biopsy-proven rejection	5 (11%)	1 (4%)
Number of rejection-free patients	N = 87	N = 98
Graft loss or deaths among rejection-free patients	7 (8%)	2 (2%)
First year post-transplant		
Number of patients with biopsy-proven rejection	N = 51	N = 35
Graft loss or deaths among pts. with previous biopsy-proven rejection	6 (12%)	3 (9%)
Number of rejection-free patients	N = 83	N = 91
Graft loss or deaths among rejection-free patients	7 (8%)	3 (3%)

Data were normalized based on the total number of "rejection-positive" and "rejection-free" patients. The one-year data are more relevant to an analysis of long term benefit. This analysis shows that patients who are rejection-free have a better chance of surviving or preserving their graft compared to those who had experienced a previous rejection episode, particularly among the Zenapax-treated population. These data supports the negative prognostic role of rejections during the first six months of kidney transplantation with respect to the loss of the allograft or patient death. This observation is consistent with one of the assumptions used to justify additional immunosuppression in kidney transplantation.
Conclusions drawn from the above analysis is also consistent with the sponsor's analysis of the effect of acute rejection on graft survival by using a time–dependent Cox regression of data censored at 1 year post-transplant. According to this analysis, in the double–therapy study, a patient's risk for graft failure after developing biopsy–proven acute rejection remained three times higher than the risk before developing rejection (relative risk = 2.98; p value = 0.002). In the triple–therapy study, a patient's risk for graft failure after developing a biopsy–proven rejection remained five times higher than the risk before developing rejection (relative risk = 5.43; p value = 0.001).

3.5 Patient survival in the first year and at 3 years post-transplant.

Neither study was powered to detect a difference in patient survival. Nonetheless, patient survival was not detrimentally affected and actually improved in Zenapax-treated patients compared with placebo patients at 6 months and 1 year post-transplant.

Phase 3 studies: Analysis of Patient Survival at 6 Months and 1 Year Post-transplant

	Study NO14874		Study NO14393	
	Placebo (N = 134)	ZENAPAX (N = 141)	Placebo (N = 134)	ZENAPAX (N = 126)
Six months post-transplant				
No. of pts alive	128 (96%)	141 (100%)	130 (97%)	125 (99%)
P value*	0.01		0.19	
One year post-transplant				
No. of pts alive	126 (94%)	140 (99%)	129 (96%)	123 (98%)
P value*	0.013		0.512	

* Unstratified logrank test.

Phase 3 studies: Summary of Primary Causes of Death during the First Year Post-transplant

	Study NO14874		Study NO14393	
	Placebo (N = 134)	ZENAPAX (N = 141)	Placebo (N = 134)	ZENAPAX (N = 126)
Total no. of pts who died	8 (6%)	1 (1%)	5 (4%)	3 (2%)
Primary Causes of Death				
Pneumonia	2 (1%)			
Septic shock	2 (1%)			
Suicide	1 (1%)	–	–	1 (1%)
Aspergillosis	–	–	1 (1%)	–
Coccidioidomycosis	–	–	1 (1%)	–
Collapse*	–	–	1 (1%)	–
Coronary artery disease	1 (1%)	–	–	–
Hemorrhage	1 (1%)	–	–	1 (1%)
Infective endocarditis	–	1 (1%)	–	–
Lymphoproliferative lymphoma	–	–	–	1 (1%)
Multiple–organ failure (sepsis)	–	–	1 (1%)	–
Myocardial infarction	1 (1%)	–	–	–
Pulmonary embolism	–	–	1 (1%)	–

*Patient, who was a diabetic, collapsed and died but no autopsy was performed.

Infection was a relatively more prominent cause of death in the placebo-treated patients. Seven of the 13 placebo patients died of infections. Only one of the four Zenapax-treated patients died of an infection, suggesting that the additional immunosppression had no major detrimental effect on the patient's immune defense.

3.6 Incidence of delayed graft function.

No significant difference was seen in the incidence of delayed graft function between the Zenapax and placebo groups in either study in the triple–therapy trial, six Zenapax patients and five placebo patients were withdrawn for delayed graft function or acute tubular necrosis after one dose of trial drug. The incidence of delayed graft function in the triple-therapy trial (no. 14393) was within the expected range for cadaveric kidney transplants.

Phase 3 studies: Analysis of Delayed Graft Function during the First 6 Months Post-transplant.

	Double–Therapy Regimen No. 14874 (cyclosporine and corticosteroids)		Triple–Therapy Regimen No. 14393 (cyclosporine, corticosteroids, and azathioprine)	
	Placebo (N=134)	**ZENAPAX (N=141)**	**Placebo (N=134)**	**ZENAPAX (N=126)**
Number of Patients with Delayed Graft Function	51 (38%)	56 (40%)	39 (29%)	27 (21%)
Pairwise Treatment Comparison				
p value*	0.78		0.18	
Odds ratio estimate of Zenapax to placebo**	1.08 (95% CI: 0.65, 1.78)		0.67 (95% CI: 0.37, 1.21)	
Treatment–by–Center Interaction				
p value ***	0.32		0.40	

*Cochran–Mantel–Haenszel test stratified by center.
**Odds of rejection on Zenapax to the odds of rejection on placebo, adjusted by center.
***Breslow and Day's test for homogeneity of odds ratio across centers.

3.7 Graft function as measured by glomerular filtration rate and serum creatinine level at 6 months, 1 year, [and 3 years] post-transplant.

Renal function was assessed at 6 months and 1 year post-transplant by measuring glomerular filtration rate and serum creatinine levels. Only the one-year data are discussed here. Note, however, that in the double–therapy study serum creatinine levels were significantly lower in the Zenapax group at both 6 months and 1 year and that a significant difference in favor of Zenapax was seen in glomerular filtration rate at 6 months post-transplant (mean 58 vs 51 mL/min, median, 53 vs 44 mL/min). No difference was seen in serum creatinine levels and glomerular filtration rate between the Zenapax group and the placebo group at 1 year post-transplant in either study. While these data indicate that there is no detrimental effect on renal function from Zenapax treatment, they further suggest that the beneficial effect of Zenapax may be transient.

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Phase 3 studies: Analysis of Graft Function at 1 Year Post-transplant

	Study No.14874		Study No.14393	
	Placebo (N = 134)	ZENAPAX (N = 141)	Placebo (N = 134)	ZENAPAX (N = 126)
Serum Creatinine Levels (mg/dL)				
No. of pts with values*	105	119	115	112
Mean	1.8	1.7	1.7	1.8
Standard error	0.06	0.05	0.07	0.07
Median	1.9	1.6	1.6	1.6
Min – Max	0.7 – 4.2	0.8 – 4.6	0.6 – 4.9	0.7 – 4.8
P value**	0.024		0.25	
Glomerular Filtration Rate (mL/min)* **				
No. of pts with values*	67	74	70	70
Mean	54	56	58	56
Standard error	3.2	2.9	3.0	2.5
Median	47	53	52	55
Min – Max	12– 155	8 – 168	15 – 139	22 – 122
P value**	0.36		0.75	

* Patients who experienced graft loss during the first 6 months post-transplant were not included in this analysis.
** Pairwise comparison of treatment using Wilcoxon rank sum test.
*** Normalized values that have been adjusted for the actual body surface area of the patient and expressed in terms of the body surface area of a standard adult male, that is, 1.73 m 2 .

3.8 Cumulative dose of prednisone in the first 6 months post-transplant and Cumulative dose of OKT3 or other anti-lymphocyte antibody therapy in the first 6 months post-transplant.

These two secondary endpoints were analyzed together. The stated rationale for looking at cumulative use of corticosteroids was that if the incidence of acute rejection was higher in the placebo group than in the Zenapax group, cumulative corticosteroid use would also be higher in the placebo group. While this endpoint is valid for the double-therapy study, it is not very informative in the triple-therapy study, because of design consideration. While investigators in the double–therapy trial were allowed to use their institution's own standard regimen for corticosteroids for both prophylaxis and treatment of rejection and to alter the dose of corticosteroids based on clinical judgement, investigators in the triple–therapy trial did not have this discretion. The design explicitly specified the dose of corticosteroids and the duration of treatment for both prophylaxis and treatment of rejection. The results show that in the double-therapy study the cumulative dose of corticosteroids in the first 6 months after transplantation was significantly higher in the placebo group than in the Zenapax group. As predicted, the cumulative dose of corticosteroids in the first 6 months after transplantation was not different between arms of the triple–therapy trial.

In both studies, the total number of days of antilymphocyte antibody therapy (OKT3, ATG, or ALG) for the treatment of rejection was similar in the two treatment arms. Neither protocol specified the dose of antilymphocyte therapy or the duration of therapy. Although the total number of days of antilymphocyte antibody therapy was similar in the two treatment arms, the proportion of Zenapax–treated patients who required antilymphocyte therapy for rejection was lower in both studies.

No formal analysis of the outcome of treatment with anti-lymphocyte therapy has been provided, nor were the data listing or the CRF available for analysis of this parameter. Because rejection-related graft losses were a smaller fraction in the Zenapax group than in the placebo group, Zenapax does not appear to hamper the ability of OKT3 (a murine IgG2a) or that of ATG to rescue a ste1roid-resistant rejection.

Phase 3 Studies. Cumulative Use of Corticosteroids and Other Antilymphocyte Antibody Therapy during the First 6 Months Post-transplant*

	Study NO14874		Study NO14393	
	Placebo (N = 134)	ZENAPAX (N = 141)	Placebo (N = 134)	ZENAPAX (N = 126)
Cumulative Dose of Corticosteroids (mg)*				
No. of pts analyzed	132	139	134	126
Mean	4438	3750	4684	4555
Standard error	232.1	168.0	174.4	165.4
Median	3622	3132	4314	4184
Min – Max	464 – 14446	750 – 17064	944 – 12938	964 – 14556
P value**	0.01		0.73	
Total No. of Days of OKT3				
No. of pts analyzed	8	5	19	9
Mean	10	8	11	9
Standard error	2.3	1.6	0.9	0.8
Median	10	9	10	10
Min – Max	1 – 20	2 – 11	1 – 18	7 – 15
P value**	0.65		0.08	
Total No. of Days of ATG or ALG				
No. of pts analyzed	14	5	2	1
Mean	13	10	7	8
Standard error	4.3	0.7	4.0	–
Median	10	10	7	8
Min – Max	4 – 68	8 –12	3 – 11	8 – 8
P value**	0.39		0.99	

* Includes use of corticosteroids for prevention as well as for treatment of rejection and use of OKT3 and ATG or ALG for treatment of rejection only.
**Pairwise comparison of treatments using Wilcoxon rank sum test.

4. USE OF ZENAPAX WITH MYCOPHENOLIC ACID MOFETIL (MMF):

HLR performed a 76–patient randomized, placebo–controlled, double–blind study in which Zenapax was added to a triple–therapy regimen including CsA (Neoral®), MMF (CellCept®), and steroids. The incidence of the combined endpoint of biopsy–proven or presumptive acute rejection was 20% (5 of 25 patients) in the placebo group and 12% (6 of 50 patients) in the Zenapax arm. The addition of Zenapax to three–drug immunosuppressive therapy did not apparently result in an increased incidence of adverse events or a change in the types of adverse events reported.
The study was not powered for efficacy nor was efficacy demonstrated, albeit the difference is in favor of Zenapax. The study limited information for safety and should exclusively be used for that purpose. No claim of efficacy of the use of Zenapax in conjunction with MMF should therefore be made.

5. PROPOSED INDICATION AND USAGE

The language in the proposed package insert states:

> *INDICATION AND USAGE: ZENAPAX is indicated for the prophylaxis of acute organ rejection in patients receiving renal transplants. It is used concomitantly with an immunosuppressive regimen, including cyclosporine and corticosteroids.*

No information regarding the use of Zenapax in a regimen without cyclosporine is available, nor Zenapax is to be used as a replacement for cyclosporine or steroids. Therefore, the indication correctly restricts its use as part of a regimen concomitantly with cyclosporine and corticosteroids. Additional wording may be required to avoid its use as a replacement for "standard" immunosuppressive therapy. Note that azathioprine (or its current replacement, mycophenolic acid mofetil) have not been mentioned under "Indication and usage". The double-therapy study support the use of Zenapax without azathioprine and therefore this statement is acceptable.

6. WARNINGS.

The language in the proposed package insert includes a simple warning and states:

> *WARNINGS: ZENAPAX should be administered under qualified medical supervision. Patients should be informed of the potential benefits of therapy and the risks associated with administration of immunosuppressive therapy. Anaphylactoid reactions following the administration of ZENAPAX have not been observed but can occur following the administration of proteins. Medications for the treatment of severe hypersensitivity reactions should, therefore, be available for immediate use. Patients on immunosuppressive therapy following transplantation are at increased risk for developing lymphoproliferative disorders and opportunistic infections.*

7. PRECAUTIONS

Immunogenicity appears not to be a concern with this humanized Ab. Minimum levels of anti-idiotypic antibodies were detected, with apparent no clinical significance. Patients with anti-idiotypic antibodies (ng/ml amount max and transient) did not experience increase rejection rates.

> *PRECAUTIONS:*
>
> *Immunogenicity: No antibodies that affected efficacy, safety, serum Zenapax levels, or any other clinically relevant parameter examined were detected.*
>
> *Drug Interactions: The following medications have been administered in clinical trials with ZENAPAX with no incremental increase in adverse reactions: cyclosporine, mycophenolate mofetil, ganciclovir, acyclovir, azathioprine, and corticosteroids.*

8. Pediatric Use Section

A study is currently ongoing to establish the safety, pharmacokinetics and limited efficacy in pediatric patients. A review of the label insert should be planned as soon as these data become available. In the mean time, all available data will be included in the final version of the package insert.

The current language in the proposed label insert states:

Pediatric Use:

9. Overdosage:

There is no clinical experience with overdosage of this agent. The porposed package in sert contains the following language:

OVERDOSAGE: There have not been any reports of overdoses with ZENAPAX. A maximum tolerated dose has not been determined in patients. A dose of 1.5 mg/kg has been administered to bone marrow transplant recipients without any associated adverse events.

10. Dosage and Administration.

Dosage and administration information are adequately presented and detailed in the porposed package insert.

DOSAGE AND ADMINISTRATION: The recommended dose for ZENAPAX is 1.0 mg/kg. The calculated volume of ZENAPAX should be mixed with 50 mL of sterile 0.9% sodium chloride solution and administered via a peripheral or central vein over a 15–minute *period. Based on the trials, the standard course of ZENAPAX therapy is five doses. The first dose should be given 24 hours before transplantation. The four remaining doses should be given at intervals of 14 days. No dosage adjustment is necessary for patients with severe renal impairment. No dosage adjustments based on other identified covariates (age, gender, proteinuria, race) are required for renal allograft patients. No data are available for administration in patients with severe hepatic impairment,*

11. CONCLUSIONS AND RECOMMENDATIONS.

The data support the efficacy of Zenapax in preventing cadaveric kidney transplant rejections when used in the context of a standard double- or triple-therapy immunosuppressive regimen.

The beneficial effect of Zenapax is demonstrable at multiple levels:

- Decreased rejection rates at six months.
- Decrease in the combined rate of biopsy-proven rejection, graft loss or death (rate of "treatment failure") at 6 months and 1 year post-transplant.
- Decreased number of rejection per patients.
- Prolonged rejection-free survival.

In addition, treatment with Zenapax was associated with:

- Increased graft survival rates at six months when included with a triple-therapy regimen. The data, however, are not statistically significant at 1 year post-transplant or for the double-therapy regimen.
- Increased patient survival rates at 6 months and 1 year post-transplant when included with a double-therapy regimen. The data, however, are not statistically for the triple-therapy regimen.
- A decreased number of patients with more than one rejection episode, albeit the difference is not statistically significant.

Zenapax appears to be associated with no significant toxicity. In particular, the incidence of infections and lymphoproliferative diseases is not increased by Zenapax, albeit data pertaining to the latter are limited in number and time of follow-up. Zenapax use does not appear to interfere with OKT3 or ATG therapy of steroid-resistant rejections.

In view of its safety profile, this reviewer finds the benefits of the use of Zenapax to outweigh its risks and recommends approval of Zenapax for the proposed indication.

File "Annotated Clinical Review 11", 11/12/97
Revised Schwieterman 12/9/97
File "Annotated Clinical Review 12", 12/19/97